

Current reviews of allergy and clinical immunology

(Supported by a grant from Astra Pharmaceuticals, Westborough, Mass)

Series editor: Harold S. Nelson, MD

Air pollution and asthma

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Asthma is a disease syndrome that has captured a great deal of attention for several years. One of the perplexing aspects to asthma is that the prevalence is increasing in most industrialized countries. The reasons for this widespread increase are largely unknown. Another aspect of industrialization is the persistence of air pollution in urban areas. Because much air pollution is due to vehicles, no solution appears in sight. The topic of this article is the association between air pollution and various signs and symptoms of asthma. Air pollution is convincingly associated with many signs of asthma aggravation. These include pulmonary function decrements, increased bronchial hyperresponsiveness, visits to emergency departments, hospital admissions, increased medication use and symptom reporting, inflammatory changes, interactions between air pollution and allergen challenges, and immune system changes. With the exception of exposure to environmental tobacco smoke, common air pollutants have not been shown to cause asthma. It seems prudent for clinicians to counsel their patients about the potential risks of asthma aggravation from common outdoor air pollutants. (*J Allergy Clin Immunol* 1999;104:717-22.)

Key words: *Asthma, air pollution, pulmonary function, airway inflammation, bronchial hyperresponsiveness*

In the past decade there has been an enhanced concern about the cardiorespiratory health effects of common outdoor air pollutants. This concern has resulted in tightening of US National Ambient Air Quality Standards for both ozone and particulate matter (PM) air pollution and in the promulgation of health-based air pollution standards in Europe and the United Kingdom. Because asthma is a disease syndrome known to be aggravated by inhaled agents, it is natural that the health effects of air pollutants in asthmatic patients has received special attention.

Outdoor air pollution levels have been associated with a broad spectrum of adverse health effects in individuals

Abbreviations used

BHR:	Bronchial hyperresponsiveness
CO:	Carbon monoxide
FVC:	Forced vital capacity
NO ₂ :	Nitrogen dioxide
PEF:	Peak expiratory flow
PFT:	Pulmonary function test
PM:	Particulate matter
PM ₁₀ :	Particulate matter ≤10 μm
SO ₂ :	Sulfur dioxide

with asthma. A listing of these adverse effects is given below:

- Pulmonary function decrements
- Increased bronchial hyperresponsiveness
- Visits to emergency departments and hospital admissions
- Increased medication use and symptom reporting
- Inflammatory changes
- Interactions between air pollution and allergen challenges
- Immune system changes

This article will describe the evidence for associations between air pollution exposure and each of the health-related end points.

PULMONARY FUNCTION DECREMENTS

Spirometry and other methods of mechanical lung function measurements have been used widely in both controlled studies of the effects of air pollution and in field epidemiologic studies of effects of ambient concentrations of air pollutants. Lung function effects have been seen after exposure to sulfur dioxide (SO₂), ozone, and PM as detailed below.

Controlled exposures

Many controlled studies exposed subjects to SO₂, after it was first shown that subjects with asthma are especially sensitive to inhaled SO₂. Inhalation of 1.0 ppm of SO₂ for 10 minutes during moderate exercise can decrease FEV₁ by 23% and increase total lung resistance by an average of 67%.¹ Investigators have shown that an exposure duration as short as 2.5 minutes is sufficient to cause SO₂-induced bronchoconstriction in subjects with asthma. Common pharmaceutical agents used to treat asthma (albuterol, cromolyn, theophylline, and corticosteroids)

From the Department of Environmental Health, University of Washington, Seattle, Wash.

Supported in part by University of Washington Center grant No. P30 ES 07033.

Received for publication June 21, 1999; revised July 19, 1999; accepted for publication July 19, 1999.

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0091-6749/99 \$8.00 + 0 1/1/101542

block or mitigate the effects of SO₂ on the airways, with albuterol being the most effective.²

Controlled exposure studies with use of ozone initially did not document a greater effect in subjects with asthma. However, as more creative experimental designs were used, it became apparent that asthma is a risk factor for bronchial response to inhaled ozone. Kreit et al³ evaluated pulmonary function changes in both healthy subjects and subjects with asthma after a 2-hour exposure to 0.40 ppm ozone. After exposure, subjects with asthma had greater pulmonary function decrements. This study also used a methacholine challenge to detect changes in bronchial hyperresponsiveness (BHR), as cited in that section of this review. Basha et al⁴ also compared the response with that of inhaled ozone between subjects with and without asthma in a controlled laboratory setting. Subjects were exposed for 6 hours to either 0.20 ppm ozone or filtered air. Bronchoalveolar lavage was performed 18 hours after exposure. Neither group showed significant changes in pulmonary function; however, the subjects with asthma showed a significant increase in BHR.

PM exposure has been very difficult to achieve in a controlled laboratory setting because PM actually is a diverse mixture of dust, smoke, and haze in the environment. Recently, instrumentation has been developed that allows an investigator to draw in ambient air and concentrate the mass of particles, thus providing a source of controlled PM for experimental exposures.⁵ Several groups have exposed healthy subjects to these concentrated air particles and generally have not seen adverse effects. To date, no studies have been carried out in subjects with asthma. However subjects with asthma have participated in controlled studies of sulfuric acid, a form of PM. As seen with SO₂ exposure, subjects with asthma are more sensitive to inhaled sulfuric acid than healthy subjects are. Decrement in FEV₁ and forced vital capacity (FVC) have been seen at concentrations as low as 35, 70, and 100 µg/m³ for durations for 30 to 40 minutes during exercise.^{6,7} These studies are of great interest because short-term concentrations of sulfuric acid in ambient air have been measured at approximately 100 µg/m³ for 1-hour peak values. Sulfuric acid is a major constituent of PM in the eastern United States and Canada.

Controlled studies with nitrogen dioxide (NO₂) exposures at realistic concentrations generally have not seen decrements in pulmonary function in either healthy subjects or subjects with asthma.

Epidemiologic studies

The primary lung function measurement used in epidemiologic studies has been peak flow (PEF) for the obvious reason that small handheld peak flow meters are convenient for use in the field. However, whenever pulmonary function measurements are made in an unsupervised situation, there is concern about proper technique and even the time of day of the measurement. The problem of verification of the time of measurement can be avoided with new computerized instruments that are available; however, the cost per unit prevents their widespread use.

A number of studies have noted changes in PEF associated with either PM or ozone. Only a handful of those studies have involved subjects with asthma. One study conducted before, during, and after the wood stove heating season in Seattle found a significant decrement in both FEV₁ and FVC associated with fine particles in 26 children with asthma.⁸ The average decline in pulmonary function was 1.8 mL/µg/m³ PM less than or equal to 2.5 µm. No significant decrements were seen in the 300 healthy children in the study. A study in Utah Valley, Utah,⁹ found a negative relationship between PM less than or equal to 10 µm (PM₁₀) and the change in PEF in subjects with asthma of widely varying ages (8-72 years).

One study in Germany reported results showing SO₂ levels associated with decrements in PEF. In that study Peters et al¹⁰ studied a panel of 155 children with asthma and 102 adults with asthma. PEF decreased an average of 0.90% (-1.35% to -0.46%) in association with an average increase of 128 µg/m³ SO₂.

Several interesting studies have evaluated lung function in children attending summer camps. The design of these studies allows daily lung function measurements by study personnel and also daily air monitoring values from a central site at the camp that is representative for all the children. In general, these studies have found linear decrements in PEF and FEV₁ associated with 1-hour average ozone concentrations. Kinney et al¹¹ summarized these studies. Analysis of 6 such studies yielded a slope of -0.50 mL in FEV₁ for each part per billion ozone concentration. This study design was repeated using children with asthma; the difference between morning and evening PEF difference was significantly correlated with daily ozone values ($r = 0.43$).¹² A recent study evaluated the effect of outdoor ozone concentrations on lung function in adults hiking on Mt Washington in New Hampshire.¹³ A total of 530 adults had their pulmonary function measured before and after hiking. The difference between prehike and posthike values in FEV₁, FVC, the FEV₁/FVC ratio, and PEF were calculated. For the group, there were average decrements in FVC and PEF (0.4% and 0.8%, respectively). Hikers with asthma or wheeze had 4-fold greater responsiveness to ozone than the group in general did.

INCREASES IN BHR

As mentioned earlier, Kriet et al³ evaluated the effects of ozone exposure in subjects with and without asthma and found an enhanced response to a methacholine provocative challenge only in the subjects with asthma. Folinsbee¹⁴ conducted a meta-analysis of studies designed to assess changes in BHR after controlled exposure to NO₂. The meta-analysis of 20 studies using subjects with asthma and 5 studies using healthy subjects found a small but significant trend of increased BHR after NO₂ exposure in subjects with asthma. On average, in the subjects with asthma there was a 60% increase in BHR after NO₂ exposure. Further evidence of increased BHR after air pollutant exposure is covered in the section on interactions between specific pollutants and allergen challenges.

VISITS TO EMERGENCY DEPARTMENTS AND HOSPITAL ADMISSIONS

There is no doubt that outdoor air pollution aggravates asthma; several outdoor pollutants have been associated with increases in visits to emergency departments for asthma. The association between increased emergency department visits for asthma and air pollution was investigated in Anchorage, Alaska,¹⁵ Reno, Nev,¹⁶ and Seattle, Wash.¹⁷ All 3 studies found significant associations between various measures of PM and increases in visits for asthma. In the Anchorage study an increase of 10 $\mu\text{g}/\text{m}^3$ PM_{10} was associated with a 3% to 6% increase in visits for asthma. In Seattle a change of 11 $\mu\text{g}/\text{m}^3$ in fine PM was associated with a 15% increase in asthma visits. The Anchorage and Reno studies did not find a significant association between emergency department visits for asthma and carbon monoxide (CO); however, CO was associated with asthma visits in Seattle. Because CO has no biologically plausible mechanism for the exacerbation of asthma, it is considered a general indicator of air pollution. In the Seattle study there was a high correlation between 24-hour CO concentrations and PM_{10} values (0.74). Other investigators have reported that the peak hourly NO_2 concentration was significantly associated with increased emergency department visits for asthma during winter months in Northern California¹⁸ and with increased emergency department visits and respiratory admissions in Athens, Greece.¹⁹ Peak hourly NO_2 was also associated with increased emergency department visits for asthma during both the winter and summer months in Barcelona, Spain.²⁰ The average peak NO_2 concentrations in the Northern California, Athens, and Barcelona studies were 69 ppb, 50 ppb, and 58 ppb, respectively. Romieu et al²¹ reported that both ozone and SO_2 were significantly associated with emergency department visits for asthma in Mexico. Also, White et al²² found that the average number of visits to an emergency department for asthma or reactive airway disease in children in Atlanta was 37% higher on days after elevated ozone episodes. A recent study of daily emergency department visits for asthma to 12 hospitals in London reported significant increases in visits associated with SO_2 , NO_2 , and PM_{10} .²³ Thus it can be seen that asthma aggravation measured by increased emergency department visits is clearly associated with outdoor concentrations of common air pollutants. Identification of the single pollutant most clearly related to the asthma visits is difficult.

Bates and Sizto²⁴ found an association between "acid summer haze" and hospital admissions for asthma in Southern Ontario. "Acid summer haze" is believed to be composed of ozone and various forms of sulfate. A study in London evaluated both air pollution and pollen effects on hospital admissions for asthma.²⁵ Ozone, NO_2 , SO_2 , and black smoke (a measure of PM) were all associated with admissions; however, there was no consistent pattern—each pollutant was significant for different age groups and lag times. There was no evidence of confounding of the associations by interaction with pollen counts. A study in Seattle found that ambient air pollu-

tion was associated with hospital admissions for asthma in patients less than 65 years old.²⁶ Asthma admissions showed a 5% increase with PM_{10} , a 4% increase with PM less than or equal to 2.5 μm , and a 6% increase with CO.

Typical correlations among the major outdoor air pollutants are shown in Table I.¹⁷ With these high correlations it is easy to understand why it is difficult to identify a single pollutant associated with health outcomes.

INCREASED SYMPTOMS AND MEDICATION USE

Air pollution is associated with increases in reports of asthma attacks and symptoms and also is associated with the duration of those attacks. The following summary will highlight some of the recent research. Asthma symptoms and medication use associated with air pollution levels have been seen in a number of different geographic locations, such as Paris,²⁷ where the strongest relationship was between asthma aggravation and SO_2 concentrations on the same day, and Sweden, where the strongest association was seen with NO_2 .²⁸ The use of medication for asthma symptoms was associated with PM_{10} in the study of Pope et al⁹ cited earlier. A study in southern California found that PM air pollution was associated with both symptoms and medication use in a panel of 25 children with asthma.²⁹ The children with the most baseline symptoms were most at risk for aggravation associated with PM. Another study in the same area found that the 12-hour average ozone concentration was associated with inhaled bronchodilator use in children with asthma.³⁰ Some studies use traffic indicators (traffic density or distance from a thoroughfare) as a surrogate for air pollution. Such studies find that these traffic indicators are associated with significant increases in adverse respiratory outcomes in children.^{31,32}

Although this review is a summary of associations between outdoor air pollutants and asthma, it should be noted that one common outdoor pollutant, NO_2 , is also a persistent indoor pollutant. There are numerous reports of increased respiratory symptoms in children exposed to NO_2 indoors as a result of emissions from gas cooking stoves.³³ A more recent study found that the use of gas cooking was significantly associated with respiratory symptoms in adult female subjects with asthma.³⁴ It should also be noted that, with regard to fine PM, many studies have shown that outdoor PM readily penetrates indoors. One study found that, in the homes of 9 children with asthma in Seattle, the average indoor/outdoor ratio of hourly values of fine PM less than 1.0 μm in diameter was 0.98.³⁵ These measurements were made during winter months in areas of the city where residential wood smoke had an impact.

INFLAMMATORY CHANGES

As noted above, subjects with asthma experience greater ozone-induced pulmonary function test (PFT) changes than do subjects without asthma. However, do

TABLE I. Bivariate correlation among exposure variables (Sept 1, 1995, to Dec 31, 1996)

	CO*	PM ₁₀ *,†	σ _{sp} *	NO ₂ ‡	NO ₂ *	SO ₂ ‡	SO ₂ *
CO*	1.00	0.74	0.74	0.47	0.66	0.15	0.32
PM ₁₀ *,†		1.00	0.82	0.56	0.66	0.24	0.43
σ _{sp} *			1.00	0.41	0.59	0.19	0.34
NO ₂ ‡				1.00	0.85	0.22	0.37
NO ₂ *					1.00	0.45	0.25
SO ₂ ‡						1.00	0.82
SO ₂ *							1.00

σ_{sp}, Light scattering coefficient.

*Daily average.

†Light scattering.

‡Daily maximum 1 hour.

they also experience a greater degree of airway inflammation? That question was addressed in a study of 19 subjects with asthma exposed to 0.2 ppm ozone for 4 hours during exercise.³⁶ In general, subjects in this study did not show greater PFT changes than normal control subjects; however, they did show greater increases in IL-8, protein, and other signs of inflammation in bronchoalveolar lavage fluid. There appeared to be no correlation between the degree of PFT change and the concentration of inflammatory mediators. The study report by Basha et al⁴ also found increased IL-8 and neutrophils in subjects with asthma after ozone exposure.

INTERACTIONS BETWEEN AIR POLLUTION AND ALLERGEN CHALLENGES

Several studies have examined the ability of air pollution exposure to enhance subsequent allergen challenges. The first study to report a positive relationship found that, in 7 subjects with asthma, ozone exposure (0.12 ppm) for 1 hour significantly reduced the concentration of ragweed or grass allergen necessary to cause a 20% decrement in FEV₁.³⁷ Since that study was published, one study has replicated these findings,³⁸ whereas one other has not.³⁹ Positive effects have been seen in the upper airways as well⁴⁰ on the basis of mediators seen in nasal lavage fluid. Exposure to NO₂ has been shown to enhance the effect of allergen in subjects with asthma. One study found an enhanced response to birch and grass pollen after NO₂ exposure⁴¹; another study found a similar response with dust mite challenge.⁴²

IMMUNE SYSTEM CHANGES

There is one report that provides evidence that seasonal ozone exposure may cause BHR as well as affect the immune system.⁴³ This study evaluated the respiratory health, allergic sensitization, and immune response in 218 children from a high ozone community (group A) and compared them with 281 children from a community with lower ozone levels (group B). BHR, measured with a methacholine challenge test, occurred more frequently in

TABLE II. Relationships of asthma end points with pollutant exposures

Asthma end point	SO ₂	NO ₂	PM	Ozone
PFTs	++	0	+	++
BHR	+/-	+	*	++
ED/admissions	*	+	++	++
Symptom/medication use	*	+	+	+
Inflammation	+/-	+/-	*	++
Allergen response†	*	+	*	+/-
Immune effects‡	*	+	*	+

+, Positive; -, negative; ED, emergency department.

*No published reports.

†Potentiation of allergen response by prior exposure to air pollutants.

‡Immune system changes associated with air pollution exposures.

the children in group A. Comparison of serum IgE levels showed no difference between the 2 groups. However, there was a significantly lower helper/suppressor T-cell ratio in group A children. One limitation of this study is the lack of personal exposure assessment because central monitors were used to estimate exposures.

INTERACTIONS BETWEEN AIR POLLUTION AND DIET

Concentrations of antioxidant vitamins in the diet and in plasma are associated with asthma status. Individuals with asthma have lower levels of serum antioxidants such as vitamins C and E and beta-carotene than the population in general does.⁴⁴⁻⁴⁶ Some studies have attempted to determine whether dietary supplementation with these vitamins would affect a subject's response to ozone. One double-blind cross-over study was designed to evaluate the effects of dietary antioxidants (400 IU vitamin E/500 mg vitamin C) on ozone-induced BHR in adult subjects with asthma.⁴⁷ Seventeen subjects were exposed to ozone (0.12 ppm) or air for 45 minutes during intermittent moderate exercise. BHR was assessed by 10-minute SO₂ (0.10 and 0.25 ppm) inhalation challenges. Vitamin treatment was associated with a lesser BHR response to SO₂ than placebo treatment as measured by forced expiratory volume in the first second (-1.2% vs 4.4%), PEF (+2.2% vs -3.0%), and mid forced expiratory flow (+2.0% vs -4.3%). These results suggest that supplementation of the diet with vitamins E and C benefits asthmatic adults exposed to air pollutants.

AIR POLLUTION AND ASTHMA CAUSATION

There is sufficient evidence that environmental tobacco smoke is a risk factor for the development of asthma.^{48,49} Also, there is evidence from occupation medicine studies that certain workplace air pollutants such as toluene diisocyanate can cause asthma.^{50,51} However, there is no consistent evidence that common air pollutants, such as those covered in this review, are involved in the development of asthma.

CONCLUSION

This review has summarized evidence that clearly shows an association between specific air pollutants and asthma aggravation. The relative strength of signs and symptoms of asthma aggravation associated with air pollutants is given in Table II. It should be noted that for NO₂ the summary pertains to indoor as well as outdoor exposures. Exposure to SO₂ causes dramatic bronchoconstriction accompanied by shortness of breath and wheezing in many subjects with asthma. Ozone exposure is associated with many signs of asthma aggravation: decreased lung function, airway inflammation, both emergency department visits and hospital admissions, and enhanced response to common aeroallergens. Particulate matter exposure is associated with decreased lung function, increased symptoms of respiratory distress, increased use of asthma medications, and unscheduled emergency department and hospital visits.

Particulate matter has been associated with numerous reports of increased mortality in individuals more than 65 years old who had pre-existing respiratory or cardiac disease. To the best of my knowledge, there have been no complete reports of an association between daily air pollutant levels and asthma fatalities. However, there was one brief report of an association between fatal asthma and ozone in New York City.⁵² Average asthma deaths were 0.7 per day for the period 1988 to 1990. Ozone was the only pollutant associated with asthma deaths with a 1-day lag between the pollutant and the death. New York City may be one of very few cities where there are enough daily asthma deaths to warrant a time series evaluation of this type. In general, asthma deaths are too rare to provide sufficient statistical power for comparisons with air pollution episodes. In conclusion, there is no doubt that air pollution is associated with asthma aggravation. We must await future research to determine whether common air pollutants can actually cause asthma. Clinicians may want to alert their patients that air pollution is one factor that can aggravate asthma. It may be useful for parents of children with asthma and adults with asthma to monitor daily air pollution concentrations when planning outdoor events.

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